Micafungin Sodium

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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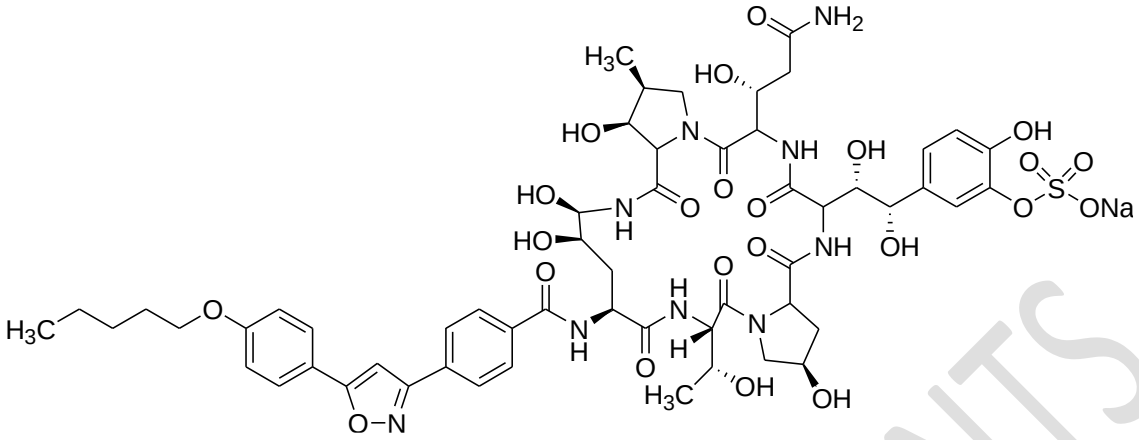
Micafungin Sodium



$C_{56}H_{70}N_9NaO_{23}S$ Mol. Wt. 1292.3

Micafungin Sodium is 1-[(4*R*,5*R*)-4,5-dihydroxy-*N*^{2}-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-l-ornithine]-4-[(4*S*)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-l-threonine]-, monosodium salt.

Micafungin Sodium contains not less than 95.0 per cent and not more than 102.0 per cent of $C_{56}H_{70}N_9NaO_{23}S$, calculated on the anhydrous and solvent-free basis.

Category. Antifungal

Description. A white or almost white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *micafungin sodium IPRS* or with the reference spectrum of micafungin sodium.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

C. It gives reaction (A) of sodium (2.3.1).

Tests

Related substances.

pH (2.4.24). 5.0 to 7.2 determined in a 10.0 per cent w/v solution.

Specific optical rotation (2.4.22). -22.0° to -20.0, determined in a 2.0 per cent w/v solution, at 20°.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the test protected to direct sunlight and use light-resistant glasswares.

Solvent mixture. 66 volumes of a buffer solution prepared by dissolving 35.8 g of *disodium hydrogen phosphate, dodecahydrate* in 1000 ml *water* and 33 volumes of a buffer solution prepared by dissolving 13.6 g of *potassium dihydrogen phosphate* in 1000 ml water, adjusted to pH 7.0.

Test solution. Dissolve 0.2 g of the substance under examination in the solvent mixture and dilute to 50.0 ml with the solvent mixture.

Reference solution (a). A 0.4 per cent w/v solution of *micafungin sodium IPRS* in the solvent mixture.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 3.0 ml of the solution to 10.0 ml with the solvent mixture.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 100.0 ml with the solvent mixture. Dilute 1.0 ml of the solution to 20.0 ml with the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as YMC-Pack ODS-AM)
- column temperature: 35°,

– mobile phase: A. a mixture of 45 volumes of *acetonitrile* and 70 volumes of a buffer solution prepared by dissolving 18.7 g of *sodium dihydrogen phosphate dihydrate* and 7.7 g of *sodium perchlorate* in 1000 ml of *water*, adjusted to pH 3.0 with 10 per cent v/v of *orthophosphoric acid*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 210 nm,
– injection volume: 2 µl.

Name	Relative retention time
Micafungin open ring analog[1]	0.73
Desmethyl micafungin[2]	0.91
Micafungin serine analog[3]	0.91
Micafungin	1.00
Micafungin epimer[4]	1.09
Deoxy micafungin[5]	1.12

[1]Sodium5-[(1*S*,2*S*,3*S*)-4-({(2*S*,3*R*)-5-amino-1-[(2*S*,3*S*,4*S*)-2-carbamoyl-3-hydroxy-4-methylpyrrolidin-1-yl]-3-hydroxy-1,5-dioxopentan-2-yl}amino)-3-[(2*S*,4*R*)-1-{[(2*S*,4*R*)-4,5-dihydroxy-1-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzoyl)pyrrolidine-2-carbonyl]-l-threonyl}-4-hydroxypyrrolidine-2-carboxamido]-1,2-dihydroxy-4-oxobutyl]-2-hydroxyphenyl sulfate,
[2]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(*R*)-1-hydroxyethyl]-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulphate,
[3]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-(hydroxymethyl)-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate,
[4]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,11*R*,12*S*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,11,12,15-tetrahydroxy-6-[(*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate,
[5]Sodium5-[(1*S*,2*S*)-2-{(2*R*,6*S*,9*S*,12*R*,14a*S*,15*S*,16*S*,20*S*,23*S*,25a*S*)-20-[(*R*)-3-amino-1-hydroxy-3-oxopropyl]-2,12,15-trihydroxy-6-[(*R*)-1-hydroxyethyl]-16-methyl-5,8,14,19,22,25-hexaoxo-9-(4-{5-[4-(pentyloxy)phenyl]isoxazol-3-yl}benzamido)tetracosahydro-1*H*-dipyrrolo[2,1-*c*:2',1'-l][1,4,7,10,13,16]hexaazacyclohenicosin-23-yl}-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate.

Inject reference solution (a), (b) and (c). The test is not valid unless the resolution between the peaks due to micafungin and micafungin epimer is not less than 1.2 in the chromatogram obtained with reference solution (a), the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (b) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (c).

Inject reference solution (b) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to micafungin open ring analog is not more than 2.66 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.8 per cent), the sum of the area of the of peaks corresponding to desmethyl micafungin and micafungin serine analog is not more than 4 times the area of the principal peak in the chromatogram obtained with reference solution (b) (1.2 per cent), the area of any peak corresponding to micafungin epimer is not more than 2.33 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent), the area of any peak corresponding to deoxy micafungin is not more than 1.66 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent) and the sum of the areas of all the secondary peaks is not more than 11.67 times the area of the principal peak in the chromatogram obtained with reference solution (b) (3.5 per cent). Ignore any peak with an area less than 0.166 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (2.3.43). Not more than 8.0 per cent, determined on 0.5 g in a mixture of 66 volumes of *formamide* and 33 volumes of *methanol*.

Bacterial endotoxins (2.2.3). Not more than 2 Endotoxin unit per mg of micafungin.

Loss on ignition (2.4.20). 4.8 to 5.8 per cent.

Assay. Determine by liquid chromatography (2.4.14).

NOTE- Carry out the test protected to direct sunlight and use light-resistant glasswares.

Solvent mixture. 30 volumes of *acetonitrile* and 70 volumes of *water.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture.

Reference solution. A 0.05 per cent w/v solution of *micafungin sodium IPRS* in the solvent mixture.

Use chromatographic system as described under Related substances with following modifications.

– injection volume: 5 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{56}H_{70}N_9NaO_{23}S$.

Microbial contamination (2.2.9). Total aerobic viable count is not more than 10^3 CFU per g and total fungal count is not more than 10^2 CFU per g.

Storage. Store protected from light and moisture at a temperature between 2° to 8°.
